

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Error
1	BRS	L1	2259	igf-1	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/1 6 11:42			0
2	BRS	L2	4478	low adj salt	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/1 6 11:42			0
3	BRS	L3	4	1 same 2	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/1 6 11:42			0
4	BRS	L4	620	"250" adj mg/ml	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/1 6 11:43			0
5	BRS	L5	836	"500" adj mg/ml	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/1 6 11:44			0
6	BRS	L6	4	1 same syrup	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/1 6 11:46			0
7	BRS	L7	4	1 same (5 or 6)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/1 6 11:47			0
8	BRS	L8	3	1 same (5 or 4)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/1 6 11:47			0
9	BRS	L9	1	1 same concentration same density same viscosity	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/1 6 11:48			0

Type	L #	Hits	Search Text	Dbs	Time Stamp	Comments	Error Definition	Error
10 BRS	L10	14	1 same microsphere	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/1 6 11:48			0
11 BRS	L11	2	1 same microsphere same plga	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/1 6 11:49			0
12 BRS	L12	125	1 same kit	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/1 6 11:51			0
13 BRS	L13	0	1 same kit same (4 or 5)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/1 6 11:51			0
14 BRS	L14	12	shirley adj bret.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/1 6 11:52			0
15 BRS	L15	18	hora adj maninder.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/1 6 11:52			0
16 BRS	L16	17	chagan adj derek.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/1 6 11:53			0
17 BRS	L17	3	(14 or 15 or 16) and 1	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/04/1 6 11:53			0

> d his

(FILE 'HOME' ENTERED AT 11:22:30 ON 16 APR 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA'  
ENTERED AT

11:23:01 ON 16 APR 2003

L1 20726 S IGF-1  
L2 15761 S LOW SALT  
L3 0 S L1 (P) L2  
L4 0 S (250 MG/ML)  
L5 1 S 250 MG PER ML  
L6 1 S 250 (W) MG (W) PER (W) ML  
L7 0 S L1 (P) (L5 OR L6)  
L8 25374 S PH (W) 5.0  
L9 2 S L8 (P) L1  
L10 1 DUPLICATE REMOVE L9 (1 DUPLICATE REMOVED)  
L11 0 S L1 (P) SYRUP  
L12 0 S L1 (P) CONCENTRATION (P) DENSITY (P) VISCOSITY  
L13 156 S L1 (P) PH  
L14 4 S L13 (P) SALT  
L15 4 DUPLICATE REMOVE L14 (0 DUPLICATES REMOVED)  
L16 4632 S PLGA  
L17 2000 S L16 (P) MICROSPHERE  
L18 9 S L1 (P) L17  
L19 3 DUPLICATE REMOVE L18 (6 DUPLICATES REMOVED)  
L20 104207 S KIT  
L21 121 S L20 (P) L1  
L22 0 S L21 (P) SYRUP

FILE 'HOME' ENTERED AT 11:22:30 ON 16 APR 2003

=> file medline caplus biosis embase scisearch agricola

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

0.21

0.21

FILE 'MEDLINE' ENTERED AT 11:23:01 ON 16 APR 2003

FILE 'CAPLUS' ENTERED AT 11:23:01 ON 16 APR 2003

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

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FILE 'BIOSIS' ENTERED AT 11:23:01 ON 16 APR 2003

COPYRIGHT (C) 2003 BIOLOGICAL ABSTRACTS INC.(R)

FILE 'EMBASE' ENTERED AT 11:23:01 ON 16 APR 2003

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FILE 'SCISEARCH' ENTERED AT 11:23:01 ON 16 APR 2003

COPYRIGHT (C) 2003 Institute for Scientific Information (ISI) (R)

FILE 'AGRICOLA' ENTERED AT 11:23:01 ON 16 APR 2003

=> s igf-1

L1 20726 IGF-1

=> s low salt

L2 15761 LOW SALT

=> s l1 (p0 l2

MISSING OPERATOR 'L7 (P0'

The search profile that was entered contains terms or nested terms that are not separated by a logical operator.

=> s l1 (p) l2

L3 0 L1 (P) L2

=> s (250 mg/ml)

'ML' IS NOT A VALID FIELD CODE

'ML' IS NOT A VALID FIELD CODE

'ML' IS NOT A VALID FIELD CODE

'ML' IS NOT A VALID FIELD CODE

L4 0 (250 MG/ML)

=> s 250 mg per ml

L5 1 250 MG PER ML

=> s 250 (w) mg (w) per (w) ml

L6 1 250 (W) MG (W) PER (W) ML

=> s l1 (p) (l5 or l6)

L7 0 L1 (P) (L5 OR L6)

=> s ph (w) 5.0

L8 25374 PH (W) 5.0

=> s l8 (p) l1

L9 2 L8 (P) L1

=> duplicate remove l9

DUPLICATE PREFERENCE IS 'MEDLINE, SCISEARCH'

KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n

PROCESSING COMPLETED FOR L9

L10 1 DUPLICATE REMOVE L9 (1 DUPLICATE REMOVED)

=> d l10 1 ibib abs

L10 ANSWER 1 OF 1 MEDLINE

DUPLICATE 1

ACCESSION NUMBER: 2001120527 MEDLINE  
 DOCUMENT NUMBER: 20567455 Entered ID: 11115387  
 TITLE: Improved recovery of insulin-like growth factors (IGFs) from bovine colostrum using alkaline diafiltration.  
 AUTHOR: Hossner K L; Yemm R S  
 CORPORATE SOURCE: Department of Animal Sciences, Colorado State University, Fort Collins, CO 80523-1171, USA.. khossner@agsci.colostate.edu  
 SOURCE: BIOTECHNOLOGY AND APPLIED BIOCHEMISTRY, (2000 Dec) 32 ( Pt 3) 161-6.  
 Journal code: 8609465. ISSN: 0885-4513.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200102  
 ENTRY DATE: Entered STN: 20010322  
 Last Updated on STN: 20010322  
 Entered Medline: 20010215

AB Studies to develop a rapid, bioprocess-compatible method to recover low-molecular-mass growth factors from bovine colostrum are reported. Defatted bovine colostrum was subjected to tangential-flow filtration (TFF) using two different filters [polyether sulphone (PES) and regenerated cellulose (RC)] at pH 5.8, pH 8.0 and pH 8.0+0.01 M NaCl. Single-pass TFF at pH 5.8 using a 100 kDa RC filter resulted in the loss of approx. 90% of insulin-like growth factor I (IGF-I) to non-specific filter adsorption. Comparison of 30 kDa RC and PES filters under single-pass conditions showed that yields of \*\*\*IGF\*\*\* - \*\*\*1\*\*\* and IGF-II were highest with RC filters. Yields of IGF-I and protein from both filter types were increased at pH 8.0 and were greatest for the 30 kDa RC filter. Effects of adding large diluent volumes continuously during TFF (diafiltration) were tested at \*\*\*pH\*\*\* \*\*\*5\*\*\* . \*\*\*0\*\*\* and 8.0. The use of 10 diafiltrate vols. at pH 8.0 resulted in the recovery of 15-28% of colostrumal \*\*\*IGF\*\*\* - \*\*\*1\*\*\* from the RC 30 kDa permeates, 2-4-fold greater than under acidic conditions. Yields of IGF-II (39.6%) were unaffected by pH and at least 97% of total protein was retained by the 30 kDa filter at pH 8.0. Denaturing SDS/PAGE analysis of the alkaline RC 30 kDa permeates demonstrated two major regions of stained proteins at 10-13 kDa and 17-19 kDa. Acidic TFF permeates contained additional stained proteins at approximately 90, 48 and 37 kDa. Isoelectric focusing of these samples demonstrated the presence of proteins with isoelectric points of 8.2 and 8.6. The current study demonstrates a one-step bioprocess-compatible technique for the recovery of low-molecular-mass polypeptides from bovine colostrum. By using alkaline diafiltration with RC filters TFF provided optimal recovery of \*\*\*IGF\*\*\* - \*\*\*1\*\*\* from colostrum.

=> d his

(FILE 'HOME' ENTERED AT 11:22:30 ON 16 APR 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT  
 11:23:01 ON 16 APR 2003

L1 20726 S IGF-1  
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 L7 0 S L1 (P) (L5 OR L6)  
 L8 25374 S PH (W) 5.0  
 L9 2 S L8 (P) L1  
 L10 1 DUPLICATE REMOVE L9 (1 DUPLICATE REMOVED)

=> s l1 (p) syrup

L11 0 L1 (P) SYRUP

=> s l1 (p) concentration (p) density (p) viscosity

L12 0 L1 (P) CONCENTRATION (P) DENSITY (P) VISCOSITY

=> s l1 (p) pH

L13 156 L1 (P) PH

=> s l13 (p) salt

L14 4 L13 (P) SALT

=> duplicate remove l14

PROCESSING COMPLETED FOR L14

L15 4 DUPLICATE REMOVE L14 (0 DUPLICATES REMOVED)

=> d l15 1-4 ibib abs

L15 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:76812 CAPLUS

DOCUMENT NUMBER: 138:131557

TITLE: Process involving cationic exchange chromatography and hydrophobic interaction chromatography for obtaining TGF.beta., IGF-1, lactoperoxidase, and immunoglobulins from milk products

INVENTOR(S): Kivits, Marinus Gerardus Cornelis; Galama, Catharina Marina; Hendriks, Andor Wilhelm Joseph

PATENT ASSIGNEE(S): Campina B.V., Neth.; Numico Research B.V.

SOURCE: PCT Int. Appl., 26 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003008447	A1	20030130	WO 2002-NL496	20020722
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: EP 2001-202794 A 20010720

EP 2001-202795 A 20010720

AB The present invention relates to a process for extg. beneficial compds., in particular growth factors, such as TGF .beta. and \*\*\*IGF\*\*\* - \*\*\*1\*\*\* from milk. In this process a hydrophobic interaction chromatog. step is included. A resin having a Bu group, or a \*\*\*Ph\*\*\* group as the ligand is used as hydrophobic interaction resin. The resin can be eluted with a \*\*\*salt\*\*\* gradient which, when the ligand is a \*\*\*Ph\*\*\* group, contains substantially no alc., and thus resulting in fractions enriched in the desired growth factors. These fractions can be sepd. further by means of a hydroxyapatite column.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:604690 CAPLUS

DOCUMENT NUMBER: 129:226609

TITLE: Refolding of improperly folded polypeptides like recombinant insulin-like growth factor recovered from inclusion bodies

INVENTOR(S): Builder, Stuart; Hart, Roger; Lester, Philip; Reifsnnyder, David

PATENT ASSIGNEE(S): Genentech, Inc., USA

SOURCE: U.S., 38 pp., Cont.-in-part of U.S. Ser. No. 110,664. CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5808006	A	19980915	US 1994-318628	19941011
US 5663304	A	19970902	US 1993-110664	19930820
WO 9506064	A1	19950302	WO 1994-US9120	19940815

W: CA, JP, US  
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRIORITY APPLN. INFO.: US 1993-110664 19930820  
WO 1994-US9120 19940815

AB A method for solubilizing and refolding peptides manufd. in bacterial hosts and accumulated as inclusion bodies is described. The method is optimized for the recovery of insulin-like growth factor and its analogs and is inexpensive. The polypeptide is resuspended at 0.1-15 mg/mL in a buffer having a \*\*\*pH\*\*\* of about 7-12 of 5-40 vol./vol.% of an alc. or polar aprotic solvent, about 0.2-3M of an alk. earth, alkali metal, or ammonium \*\*\*salt\*\*\*, about 0.1-9M of a chaotropic agent, and about 0.10-15 .mu.M of a copper or manganese \*\*\*salt\*\*\*. The protein is allowed to refold by incubating it in this buffer. The presence of the low concns. of copper or manganese minimizes the formation of incorrectly folded proteins and avoids the need for disulfide exchange agents. The method can also be used in two-phase systems where cell lysates are fractionated by phase partition and the phase contg. the inclusion bodies is under conditions suitable for solubilization and renaturation. The method is demonstrated with \*\*\*IGF\*\*\* - \*\*\*1\*\*\* manufd. in Escherichia coli by expression of a cDNA. From a large-scale fermn. (600-800 L) the protein could be refolded with a recovery of .apprx.50%. Expts. using two-phase systems are reported.

REFERENCE COUNT: 112 THERE ARE 112 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1997:547305 CAPLUS

DOCUMENT NUMBER: 127:149410

TITLE: Preparation of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues

INVENTOR(S): Carpino, Philip A.; Jardine, Dasilva Paul A.; Lefker, Bruce A.; Ragan, John A.

PATENT ASSIGNEE(S): Pfizer Inc., USA; Carpino, Philip A.; Jardine, Dasilva Paul A.; Lefker, Bruce A.; Ragan, John A.

SOURCE: PCT Int. Appl., 152 pp.  
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9724369	A1	19970710	WO 1996-IB1353	19961204
W: AU, BG, BR, BY, CA, CN, CZ, HU, IL, IS, JP, KR, KZ, LK, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
TW 432073	B	20010501	TW 1996-85113857	19961113
CA 2241725	AA	19970710	CA 1996-2241725	19961204
AU 9675850	A1	19970728	AU 1996-75850	19961204
AU 716934	B2	20000309		
EP 869968	A1	19981014	EP 1996-938434	19961204
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LV, FI, RO				
CN 1206422	A	19990127	CN 1996-199388	19961204
JP 11501945	T2	19990216	JP 1996-524124	19961204
BR 9612465	A	19990713	BR 1996-12465	19961204
JP 2001213800	A2	20010807	JP 2000-386997	19961204
RU 2172742	C2	20010827	RU 1998-112108	19961204
ZA 9610858	A	19980623	ZA 1996-10858	19961223
NO 9802991	A	19980826	NO 1998-2991	19980626
US 6107306	A	20000822	US 1999-259691	19990301
US 6110932	A	20000829	US 1999-258956	19990301
US 6124264	A	20000926	US 1999-259776	19990301
US 6278000	B1	20010821	US 1999-470668	19991222

US 6306875	B1	20011023	US 2000-593582	20000633
US 6313140	B1	20011026	US 2000-593581	20000633
US 2002049196	A1	20020425	US 2000-734274	20001211
US 6482825	B2	20021119		

PRIORITY APPLN. INFO.:

US 1995-9469P	P	19951228
JP 1997-524124	A3	19961204
WO 1996-IB1353	W	19961204
US 1998-68566	A3	19980521
US 1999-258956	A1	19990301
US 1999-259691	A1	19990301
US 1999-259776	A3	19990301

OTHER SOURCE(S): MARPAT 127:149410

GI

/ Structure 1 in file .gra /

AB Title compds. I [X = CH<sub>2</sub>, bond; X<sub>1</sub>, X<sub>2</sub> = independently bond, CH<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>; Y = O, S; R<sub>1</sub> = H, CN, side chain such as (un)substituted (CH<sub>2</sub>)<sub>q</sub>N(X<sub>6</sub>)R, (CH<sub>2</sub>)<sub>t</sub>A<sub>1</sub>, etc.; q = 0-4, t = 0-3; X<sub>6</sub> = H, (un)substituted C<sub>1</sub>-6 alkyl, C<sub>3</sub>-7 cycloalkyl, etc; A<sub>1</sub> = (un)substituted C<sub>5</sub>-7 cycloalkenyl, \*\*\*Ph\*\*\*, 4-8 membered heterocycle, etc.; R<sub>2</sub> = H, (un)substituted C<sub>1</sub>-8 alkyl, C<sub>0</sub>-3 alkyl-C<sub>3</sub>-8 cycloalkyl, C<sub>1</sub>-4 alkyl-A<sub>1</sub>; R<sub>3</sub> = (un)substituted A<sub>1</sub>, C<sub>1</sub>-10 alkyl, C<sub>1</sub>-6 alkyl-A<sub>1</sub>, C<sub>1</sub>-6 alkyl-C<sub>3</sub>-7 cycloalkyl, etc; R<sub>4</sub> = H, (un)substituted C<sub>1</sub>-6 alkyl, C<sub>3</sub>-7 cycloalkyl; or R<sub>3</sub> and R<sub>4</sub> form a ring; X<sub>4</sub> = H, C<sub>1</sub>-6 alkyl; or X<sub>4</sub> and R<sub>4</sub> form a ring; R<sub>6</sub> = bond, Z<sub>1</sub>(CH<sub>2</sub>)<sub>a</sub>C(X<sub>5</sub>)(X<sub>5a</sub>)(CH<sub>2</sub>)<sub>b</sub>; a = 0-3; b = 0-3; X<sub>5</sub>, X<sub>5a</sub> = independently H, CF<sub>3</sub>, A<sub>1</sub>, (un)substituted C<sub>1</sub>-6 alkyl, or form a ring; Z<sub>1</sub> = bond, O, NX<sub>12</sub>, X<sub>12</sub> = H, (un)substituted C<sub>1</sub>-6 alkyl; R<sub>7</sub>, R<sub>8</sub> = independently (un)substituted C<sub>1</sub>-6 alkyl, or form a ring] and pharmaceutically-acceptable \*\*\*salts\*\*\* thereof, are growth hormone secretagogues and increase the level of endogenous growth hormone. These compds. are useful for the treatment and prevention of osteoporosis, congestive heart failure, frailty assocd. with aging, obesity; accelerating bone fracture repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating the recovery of burn patients or patients having undergone major surgery; improving muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis or renal homeostasis. These compds. are also useful in treating osteoporosis when used in combination with: a bisphosphonate compd. such as alendronate; estrogen, premarin, and optionally progesterone; an estrogen agonist or antagonist; or calcitonin, and pharmaceutical compns. useful therefor. Further, the present invention is directed to pharmaceutical compns. useful for increasing the endogenous prodn. or release of growth hormone in a human or other animal which comprises an effective amt. of a compd. of the present invention and a growth hormone secretagogue selected from GHRP-6, Hexarelin, GHRP-1, growth hormone releasing factor (GRF), \*\*\*IGF\*\*\* - \*\*\*1\*\*\*, IGF-2 or B-HT920. The invention is also directed to intermediates useful in the prepn. of I. Thus, alkylation of oxopiperidinecarboxylate ester II (Boc = Me<sub>3</sub>CO<sub>2</sub>C) (prepn. given) with PhCH<sub>2</sub>Br, followed by cyclocondensation with MeNHNH<sub>2</sub> and deprotection gave pyrazolopyridinone III. Amidation of Boc-Aib-D-Ser(CH<sub>2</sub>Ph)-OH (prepn. given) with III, diastereomer sepn., and deprotection, gave sepd. title compds. IV as their HCl \*\*\*salts\*\*\*.

L15 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1995:623433 CAPLUS

DOCUMENT NUMBER: 123:27196

TITLE: Refolding of improperly folded polypeptides like recombinant insulin-like growth factor recovered from inclusion bodies

INVENTOR(S): Builder, Stuart; Hart, Roger; Lester, Phillip; Reifsnnyder, David

PATENT ASSIGNEE(S): Genetech, Inc., USA

SOURCE: PCT Int. Appl., 74 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2



## PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9506064	A1	19950302	WO 1994-US9120	19940815
W: CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5663304	A	19970902	US 1993-110664	19930820
CA 2168552	AA	19950302	CA 1994-2168552	19940815
EP 714406	A1	19960605	EP 1994-927917	19940815
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 09501693	T2	19970218	JP 1994-507626	19940815
US 5808006	A	19980915	US 1994-318628	19941011
US 5756672	A	19980526	US 1995-470108	19950606

## PRIORITY APPLN. INFO.:

US 1993-110664	19930820
WO 1994-US9120	19940815

AB A method for solubilizing and refolding peptides manufd. in bacterial hosts and accumulated as inclusion bodies is described. The method is optimized for the recovery of insulin-like growth factor and its analogs and is inexpensive. The polypeptide is resuspended at 0.1 - 15 mg/mL in a buffer having a \*\*\*pH\*\*\* of about 7-12 of 5-40 vol.% of an alc. or polar aprotic solvent, about 0.2 to 3 M of an alk. earth, alkali metal, or ammonium \*\*\*salt\*\*\*, about 0.1 to 9 M of a chaotropic agent, and about 0.10 to 15 .mu.M of a copper or manganese \*\*\*salt\*\*\*. The protein is allowed to refold by incubating it in this buffer. The presence of the low concns. of copper or manganese minimizes the formation of incorrectly folded proteins and avoids the need for disulfide exchange agents. The method can also be used in two-phase systems where cell lysates are fractionated by phase partition and the phase contg. the inclusion bodies is under conditions suitable for solubilization and renaturation. The method is demonstrated with \*\*\*IGF\*\*\* - \*\*\*1\*\*\* manufd. in Escherichia coli by expression of a cDNA. From a large-scale fermn. (600-800 L) the protein could be refolded with a recovery of about 50%. Expts. using two-phase systems are reported.

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FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 11:23:01 ON 16 APR 2003

L1	20726 S IGF-1
L2	15761 S LOW SALT
L3	0 S L1 (P) L2
L4	0 S (250 MG/ML)
L5	1 S 250 MG PER ML
L6	1 S 250 (W) MG (W) PER (W) ML
L7	0 S L1 (P) (L5 OR L6)
L8	25374 S PH (W) 5.0
L9	2 S L8 (P) L1
L10	1 DUPLICATE REMOVE L9 (1 DUPLICATE REMOVED)
L11	0 S L1 (P) SYRUP
L12	0 S L1 (P) CONCENTRATION (P) DENSITY (P) VISCOSITY
L13	156 S L1 (P) PH
L14	4 S L13 (P) SALT
L15	4 DUPLICATE REMOVE L14 (0 DUPLICATES REMOVED)

=> s plga

L16 4632 PLGA

=> s l16 (p) microsphere

L17 2000 L16 (P) MICROSPHERE

=> s l1 (p) l17

L18 9 L1 (P) L17

=> duplicate remove l18

DUPLICATE PREFERENCE IS 'MEDLINE, EMBASE, SCISEARCH'

KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n

PROCESSING COMPLETED FOR L18

L19 3 DUPLICATE REMOVE L18 (6 DUPLICATES REMOVED)

=> d 119 1-3 ibib abs

L19 ANSWER 1 OF 3 MEDLINE DUPLICATE 1  
ACCESSION NUMBER: 2000267100 MEDLINE  
DOCUMENT NUMBER: 20267100 PubMed ID: 10809103  
TITLE: De novo adipose tissue generation through long-term, local delivery of insulin and insulin-like growth factor-1 by PLGA/PEG microspheres in an in vivo rat model: a novel concept and capability.  
AUTHOR: Yuksel E; Weinfeld A B; Cleek R; Waugh J M; Jensen J; Boutros S; Shenag S M; Spira M  
CORPORATE SOURCE: Division of Plastic Surgery at Baylor College of Medicine, Houston, Texas, USA.. eyuksel@bcm.tmc.edu  
SOURCE: PLASTIC AND RECONSTRUCTIVE SURGERY, (2000 Apr) 105 (5) 1721-9.  
Journal code: 1306050. ISSN: 0032-1052.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
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ENTRY MONTH: 200005  
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AB This study was undertaken to characterize the duration of long-term growth factor delivery by poly(lactic-co-glycolic-acid)-polyethylene glycol ( \*\*\*PLGA\*\*\* /PEG) \*\*\*microspheres\*\*\* and to evaluate the potential of long-term delivery of insulin and insulin-like growth factor-1 ( \*\*\*IGF\*\*\* - \*\*\*1\*\*\* ) for the de novo generation of adipose tissue in vivo. \*\*\*PLGA\*\*\* /PEG \*\*\*microspheres\*\*\* containing insulin and \*\*\*IGF\*\*\* - \*\*\*1\*\*\* , separately, were produced by a double-emulsion solvent-extraction technique. In the first phase of the experiment, the in vitro release kinetics of the \*\*\*microspheres\*\*\* were evaluated for the optical density and polyacrylamide gel electrophoresis of solutions incubated with insulin-containing \*\*\*microspheres\*\*\* for four different periods of time (n = 1). The finding of increased concentrations of soluble insulin with increased incubation time confirmed continual protein release. In the second stage of the experiment, 16 rats were divided equally into four study groups (insulin, \*\*\*IGF\*\*\* - \*\*\*1\*\*\* , insulin + \*\*\*IGF\*\*\* - \*\*\*1\*\*\* , and blank \*\*\*microspheres\*\*\* ) (n = 4). Insulin and \*\*\*IGF\*\*\* - \*\*\*1\*\*\* containing \*\*\*microspheres\*\*\* were administered directly to the deep muscular fascia of the rat abdominal wall to evaluate the potential for de novo adipose tissue generation via adipogenic differentiation from native nonadipocyte cell pools in vivo. Animals treated with blank \*\*\*microspheres\*\*\* served as an external control group. At the 4-week harvest period, multiple ectopic islands of adipose tissue were observed on the abdominal wall of the animals treated with insulin, \*\*\*IGF\*\*\* - \*\*\*1\*\*\* , and insulin + \*\*\*IGF\*\*\* - \*\*\*1\*\*\* \*\*\*microspheres\*\*\* . Such islands were not seen in the blank \*\*\*microsphere\*\*\* group. Hematoxylin and eosin-stained sections of the growth factor groups demonstrated mature adipocytes interspersed with fibrous tissue superficial to the abdominal wall musculature and continuous with the fascia. Oil-Red-O stained sections demonstrated that these cells contained lipid. Computer-aided image analysis of histologic sections confirmed that there were statistically significant increases in the amount of "ectopic" adipose neotissue developed on the abdominal wall of animals treated with growth factor \*\*\*microspheres\*\*\* . In conclusion, this study confirms the long-term release of proteins from \*\*\*PLGA\*\*\* /PEG \*\*\*microspheres\*\*\* up to 4 weeks and demonstrates the potential of long-term local insulin and \*\*\*IGF\*\*\* - \*\*\*1\*\*\* to induce adipogenic differentiation to mature lipid-containing adipocytes from nonadipocyte cell pools in vivo at 4 weeks.

L19 ANSWER 2 OF 3 MEDLINE DUPLICATE 2  
ACCESSION NUMBER: 2000267099 MEDLINE  
DOCUMENT NUMBER: 20267099 PubMed ID: 10809102  
TITLE: Increased free fat-graft survival with the long-term, local delivery of insulin, insulin-like growth factor-I, and basic fibroblast growth factor by PLGA/PEG microspheres.  
AUTHOR: Yuksel E; Weinfeld A B; Cleek R; Wamsley S; Jensen J;

CORPORATE SOURCE: Boutros S; Waugh J M; Shenag S M; Spira M  
Division of Plastic Surgery at Baylor College of Medicine,  
Houston, Texas, USA.. eyuksel@bcm.tmc.edu  
SOURCE: PLASTIC AND RECONSTRUCTIVE SURGERY, (2000 Apr) 105 (5)  
1712-20.  
Journal code: 1306050. ISSN: 0032-1052.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 200005  
ENTRY DATE: Entered STN: 20000606  
Last Updated on STN: 20000606  
Entered Medline: 20000519

AB The present investigation evaluates the effects of long-term, local delivery of insulin, insulin-like growth factor-1 ( \*\*\*IGF\*\*\* - \*\*\*1\*\*\* ), and basic fibroblast growth factor (bFGF) on fat-graft survival using a poly (lactic-co-glycolic-acid)-polyethylene glycol ( \*\*\*PLGA\*\*\* /PEG) \*\*\*microsphere\*\*\* delivery system. Twelve-micrometer \*\*\*PLGA\*\*\* /PEG \*\*\*microspheres\*\*\* incorporated separately with insulin, \*\*\*IGF\*\*\* - \*\*\*1\*\*\* , and bFGF were manufactured using a double-emulsion solvent-extraction technique. Inguinal fat from Sprague Dawley rats was harvested, diced, washed, and mixed with (1) insulin \*\*\*microspheres\*\*\* , (2) insulin-like growth factor-1 \*\*\*microspheres\*\*\* , (3) basic fibroblast growth factor \*\*\*microspheres\*\*\* , (4) a combination of the insulin and \*\*\*IGF\*\*\* - \*\*\*1\*\*\* \*\*\*microspheres\*\*\* , and (5) a combination of insulin, \*\*\*IGF\*\*\* - \*\*\*1\*\*\* , and bFGF \*\*\*microspheres\*\*\* . The treated fat grafts were implanted autologously into subdermal pockets in six animals for each group. Animals receiving untreated fat grafts and fat grafts treated with blank \*\*\*microspheres\*\*\* constituted two external control groups (six animals per external control group). At 12 weeks, all fat-graft groups were compared on the basis of weight maintenance and a histomorphometric analysis of adipocyte area percentage, indices of volume retention and cell composition, respectively. Weight maintenance was defined as the final graft weight as a percent of the implanted graft weight. All growth factor treatments significantly increased fat-graft weight maintenance objectively, and volume maintenance grossly, in comparison with the untreated and blank \*\*\*microsphere\*\*\* -treated controls. Treatment with insulin and \*\*\*IGF\*\*\* - \*\*\*1\*\*\* , alone or in combination, was found to increase the adipocyte area percentage in comparison with fat grafts treated with bFGF alone or in combination with other growth factors. In conclusion, the findings of this study indicate that long-term, local delivery of growth factors with \*\*\*PLGA\*\*\* /PEG \*\*\*microspheres\*\*\* has the potential to increase fat-graft survival rates. Further, the type of growth factor delivered may influence the cellular/stromal composition of the grafted tissue.

L19 ANSWER 3 OF 3 MEDLINE DUPLICATE 3  
ACCESSION NUMBER: 2000415295 MEDLINE  
DOCUMENT NUMBER: 20401760 PubMed ID: 10946936  
TITLE: Augmentation of adipofascial flaps using the long-term local delivery of insulin and insulin-like growth factor-1.  
AUTHOR: Yuksel E; Weinfeld A B; Cleek R; Jensen J; Wamsley S; Waugh J M; Spira M; Shenag S  
CORPORATE SOURCE: Division of Plastic Surgery, Baylor College of Medicine, and the Institute of Bioengineering and Bioscience, Rice University, Houston, Texas, USA.  
SOURCE: PLASTIC AND RECONSTRUCTIVE SURGERY, (2000 Aug) 106 (2) 373-82.  
Journal code: 1306050. ISSN: 0032-1052.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 200008  
ENTRY DATE: Entered STN: 20000907  
Last Updated on STN: 20000907  
Entered Medline: 20000828

AB The adipofascial flaps currently described in the literature frequently lack the volume requirements for reconstructive goals. In this study, the authors examined the use of long-term local delivery of insulin and

insulin-like growth factor-1 ( \*\*\*IGF\*\*\* - \*\*\*1\*\*\* ) using poly(lactic-co-glycolic acid) (PLGA) ( \*\*\*PLGA\*\*\* ) PEG) \*\*\*microspheres\*\*\* to augment inguinal adipofascial flaps based on the inferior epigastric vessels in the rat. Two flap models, the island flap and the limited dissection flap, were used to demonstrate simultaneous treatment and pretreatment modalities, respectively. Experimental groups received 12.5 mg of insulin \*\*\*microspheres\*\*\* (carrying 1 IU of insulin) plus 12.5 mg of \*\*\*IGF\*\*\* - \*\*\*1\*\*\* \*\*\*microspheres\*\*\* (carrying 2.5 microg of \*\*\*IGF\*\*\* - \*\*\*1\*\*\* ). A group undergoing the operation only (no treatment with \*\*\*microspheres\*\*\* ) and a group treated with blank \*\*\*microspheres\*\*\* (no growth factor) served as external controls for the surgical procedure and the drug delivery device, respectively. In all groups (n = 5 animals in each), the contralateral flap served as an internal control. Upon harvest on postoperative day 28, the insulin and \*\*\*IGF\*\*\* - \*\*\*1\*\*\* -treated flaps in both models weighed statistically more than the internal control flaps and the two external control flaps. Likewise, on gross inspection, the adipogenic growth factor-treated flaps had greater volumes than the internal control flap groups and both of the external control flap groups (operation only and blank \*\*\*microspheres\*\*\* ). Other intergroup comparisons suggested the absence of a systemic insulin and \*\*\*IGF\*\*\* - \*\*\*1\*\*\* effect on adiposity. A histomorphometric analysis suggested (1) that insulin and \*\*\*IGF\*\*\* - \*\*\*1\*\*\* treatment does not alter flap cell composition and (2) that flap augmentation is secondary to the stimulation of cell proliferation and adipocytic differentiation rather than the hypertrophy of mature adipocytes. Further evidence in favor of cell proliferation and differentiation was the discovery of nonanatomic, ectopic fat islands on the pedicle sheath of the treated flaps and the lack of variation in cell size distribution among groups. The authors concluded that the long-term local delivery of insulin and \*\*\*IGF\*\*\* - \*\*\*1\*\*\* with \*\*\*PLGA\*\*\* /PEG \*\*\*microspheres\*\*\* is an effective method of adipofascial flap augmentation; this method increases the number of mature adipocytes rather than increasing the size of preexisting cells.

=> d his

(FILE 'HOME' ENTERED AT 11:22:30 ON 16 APR 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 11:23:01 ON 16 APR 2003

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L1      20726 S IGF-1 .
L2      15761 S LOW SALT
L3          0 S L1 (P) L2
L4          0 S (250 MG/ML)
L5          1 S 250 MG PER ML
L6          1 S 250 (W) MG (W) PER (W) ML
L7          0 S L1 (P) (L5 OR L6)
L8      25374 S PH (W) 5.0
L9          2 S L8 (P) L1
L10         1 DUPLICATE REMOVE L9 (1 DUPLICATE REMOVED)
L11         0 S L1 (P) SYRUP
L12         0 S L1 (P) CONCENTRATION (P) DENSITY (P) VISCOSITY
L13        156 S L1 (P) PH
L14         4 S L13 (P) SALT
L15         4 DUPLICATE REMOVE L14 (0 DUPLICATES REMOVED)
L16        4632 S PLGA
L17        2000 S L16 (P) MICROSPHERE
L18         9 S L1 (P) L17
L19         3 DUPLICATE REMOVE L18 (6 DUPLICATES REMOVED)
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=> s kit

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L20      104207 KIT
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=> s l20 (p) l1

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L21      121 L20 (P) L1
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=> s l21 (p) syrup

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L22         0 L21 (P) SYRUP
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=> d his

(FILE 'HOME' ENTERED AT 11:23:30 ON 16 APR 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT  
11:23:01 ON 16 APR 2003

L1 20726 S IGF-1  
L2 15761 S LOW SALT  
L3 0 S L1 (P) L2  
L4 0 S (250 MG/ML)  
L5 1 S 250 MG PER ML  
L6 1 S 250 (W) MG (W) PER (W) ML  
L7 0 S L1 (P) (L5 OR L6)  
L8 25374 S PH (W) 5.0  
L9 2 S L8 (P) L1  
L10 1 DUPLICATE REMOVE L9 (1 DUPLICATE REMOVED)  
L11 0 S L1 (P) SYRUP  
L12 0 S L1 (P) CONCENTRATION (P) DENSITY (P) VISCOSITY  
L13 156 S L1 (P) PH  
L14 4 S L13 (P) SALT  
L15 4 DUPLICATE REMOVE L14 (0 DUPLICATES REMOVED)  
L16 4632 S PLGA  
L17 2000 S L16 (P) MICROSPHERE  
L18 9 S L1 (P) L17  
L19 3 DUPLICATE REMOVE L18 (6 DUPLICATES REMOVED)  
L20 104207 S KIT  
L21 121 S L20 (P) L1  
L22 0 S L21 (P) SYRUP

=> log y

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	67.95	68.16
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